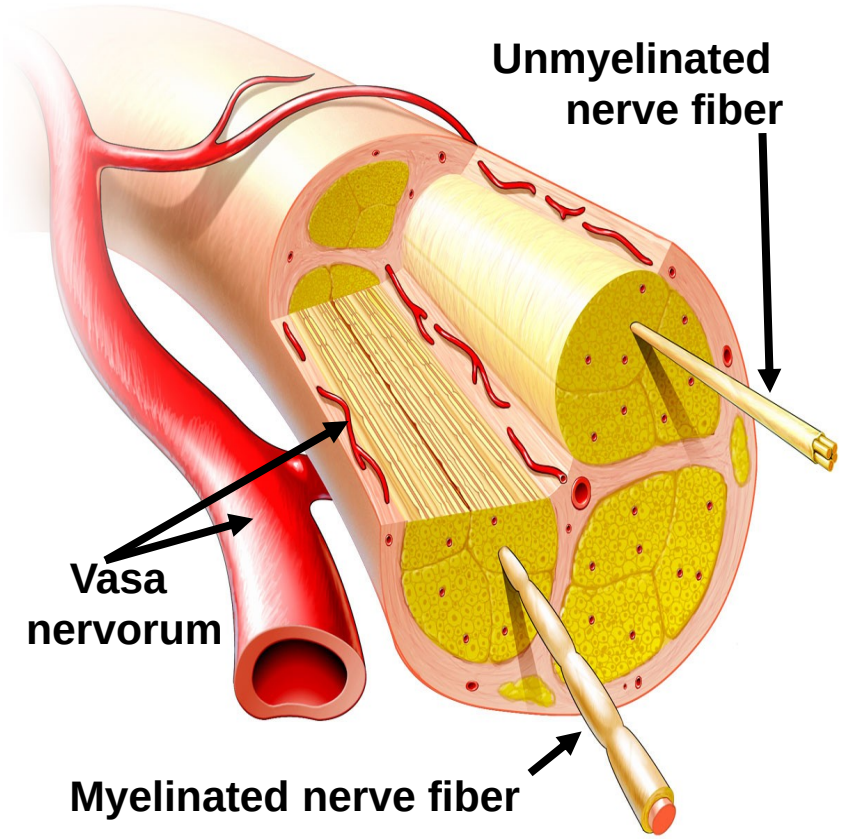
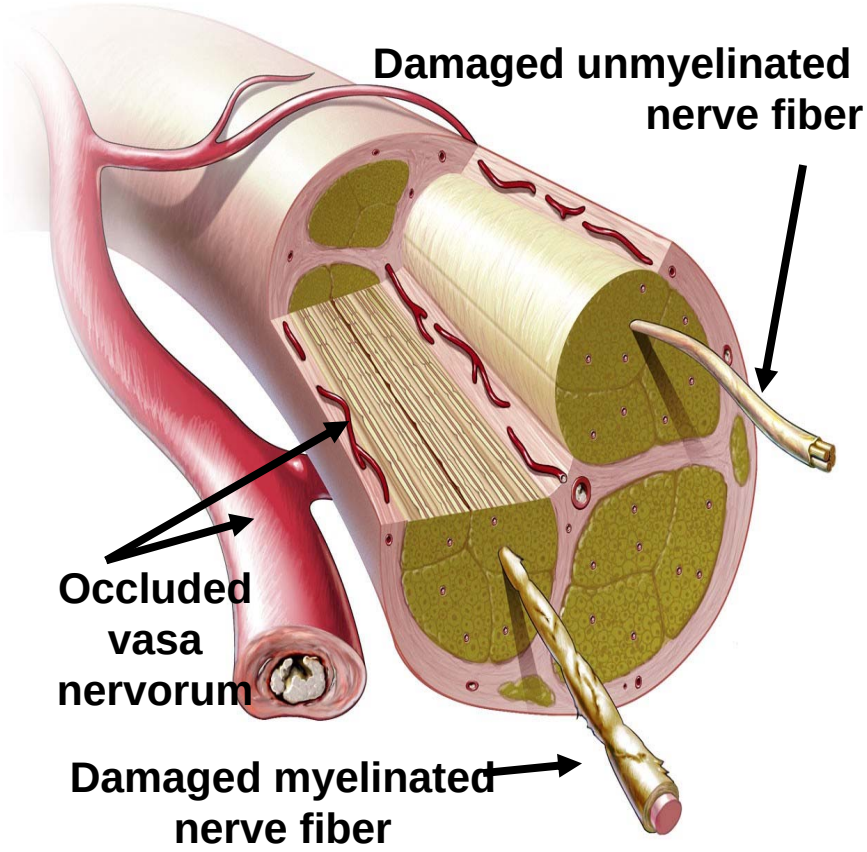
Diabetic Peripheral Neuropathy

Healthy Nerves and Blood Vessels



Nerves and Blood Vessels Damaged by DPN



Lessons Learned from Failed Clinical Trials in Diabetic Neuropathy

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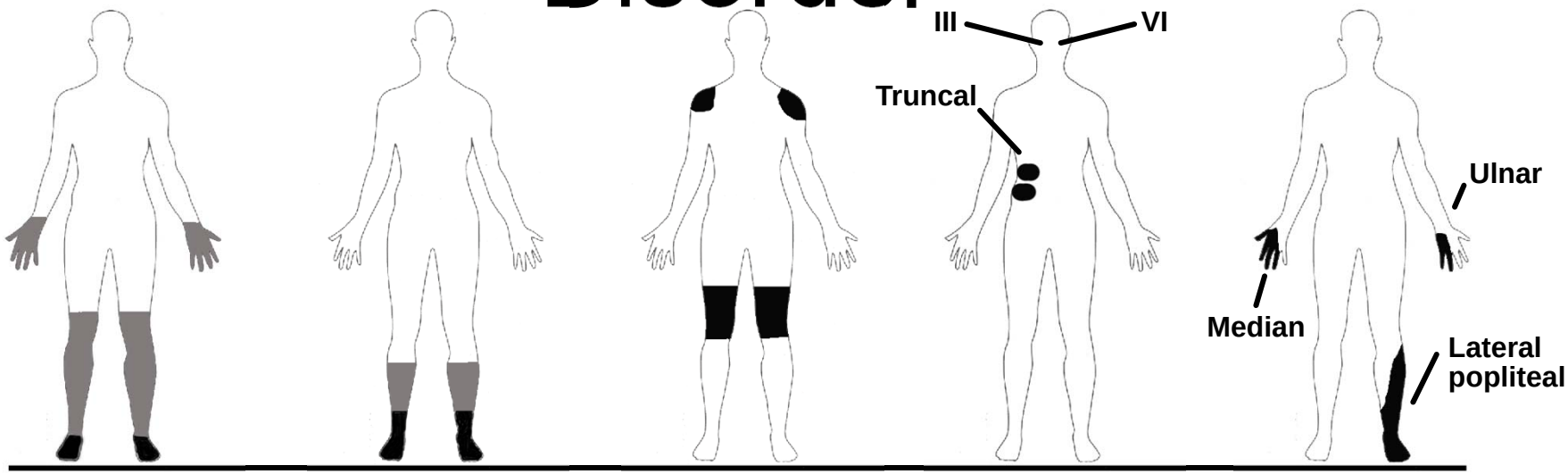
THE STRELITZ DIABETES CENTER

Diabetic Neuropathies are NOT a Single Homogenous Disorder



Large-fiber neuropathy	Small-fiber neuropathy	Proximal neuropathy	Acute mono neuropathies	Entrapment neuropathies
Sensory loss: 0 – +++ (touch vibration)	Sensory loss: 0 – + (thermal allodynia)	Sensory loss: 0 – +	Sensory loss: 0 – +	Sensory loss in nerve distribution: + – +++
Pain: + – +++	Pain: + – +++	Pain: + – +++	Pain: + – +++	Pain: + – ++
Tendon reflex: N – ↓↓↓	Tendon reflex: N – ↓	Tendon reflex: ↓↓	Tendon reflex: N	Tendon reflex: N
Motor deficit: 0 – +++	Motor deficit: 0	Proximal motor deficit: + – +++	Motor deficit: + – +++	Motor deficit: + – +++

N, normal.

Modified from Vinik A, et al. *Diabetologia*. 2008;24:407.

And What We Mistake for Diabetic Neuropathy

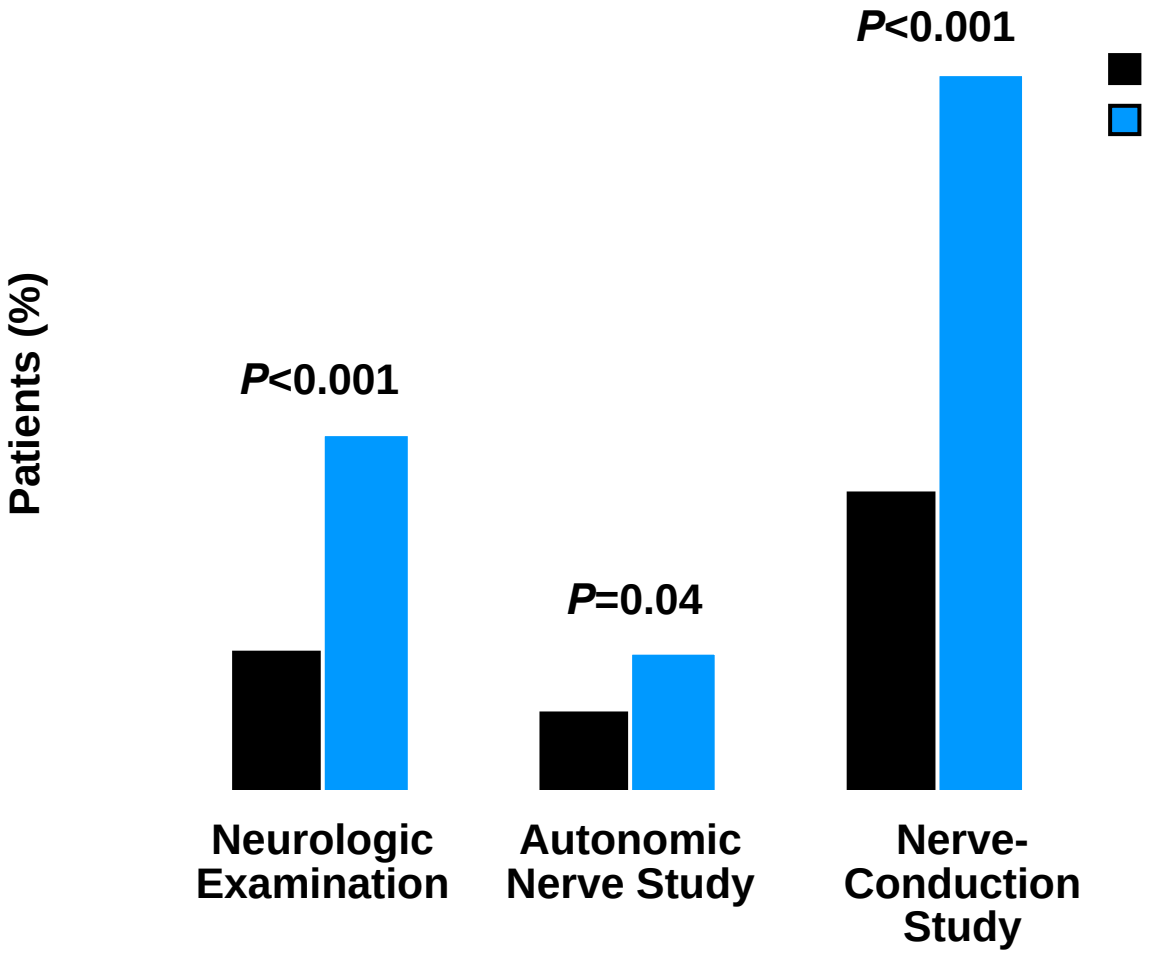
- Claudication
- Morton’s neuroma
- Osteoarthritis
- Radiculopathy
- Plantar fasciitis
- Fibromyalgia
- Tarsal tunnel syndrome

Why have we Failed to Demonstrate Efficacy of Therapy in Diabetic Neuropathy

- **Interventions are not efficacious;**
- **Present diabetes care inhibits development of complications;**
- **Other diabetic complications (hypertension, hyperlipidemia, renal disease, and other) with possible adverse effects on DSPN are now managed better;**
- **The wrong kind, stage, duration, speed of evolution of DSPN is studied;**
- **End points chosen are insufficiently sensitive, specific, monotonic**
- **Combining measures of small and large fiber function may obscure an effect on one or other**
- **Translating (measuring a consistent trend of worsening or improvement with time) to many medical centers hazardous**
- **Excessive recruitment of type 2 diabetic patients showing little change with time and excessive variability of measured end points**
- **Both placebo and treated patients receive better than usual medical treatment while**

***Modified from Dyck et al. Diabetes Care* 30:2619–2625, 2007**

Glycemic Control in Type 1 Diabetes Prevents Neuropathy

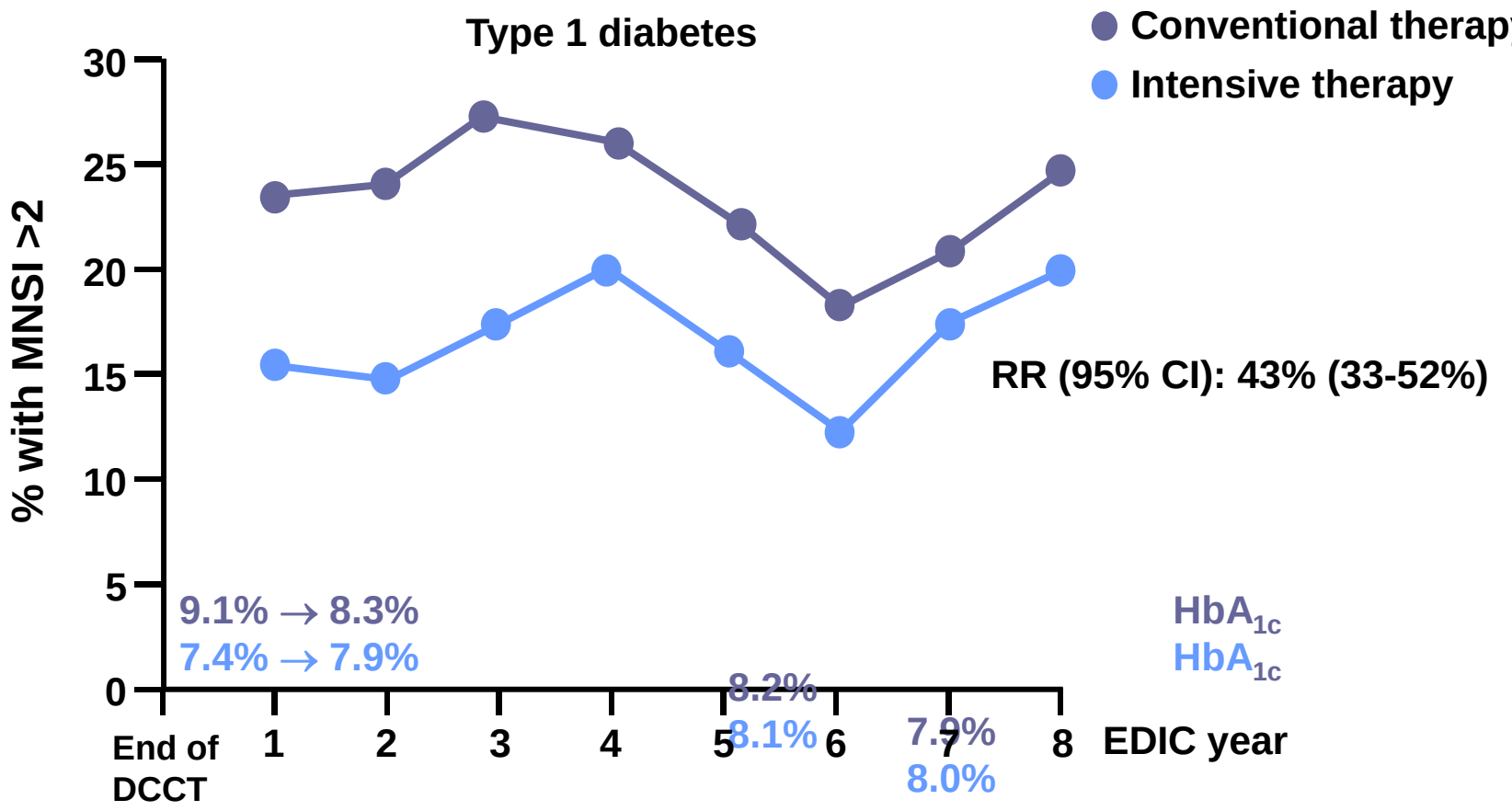


The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;329:977.

Epidemiology of diabetes intervention and complications (EDIC) study in type 1 diabetes

Metabolic Memory Counts

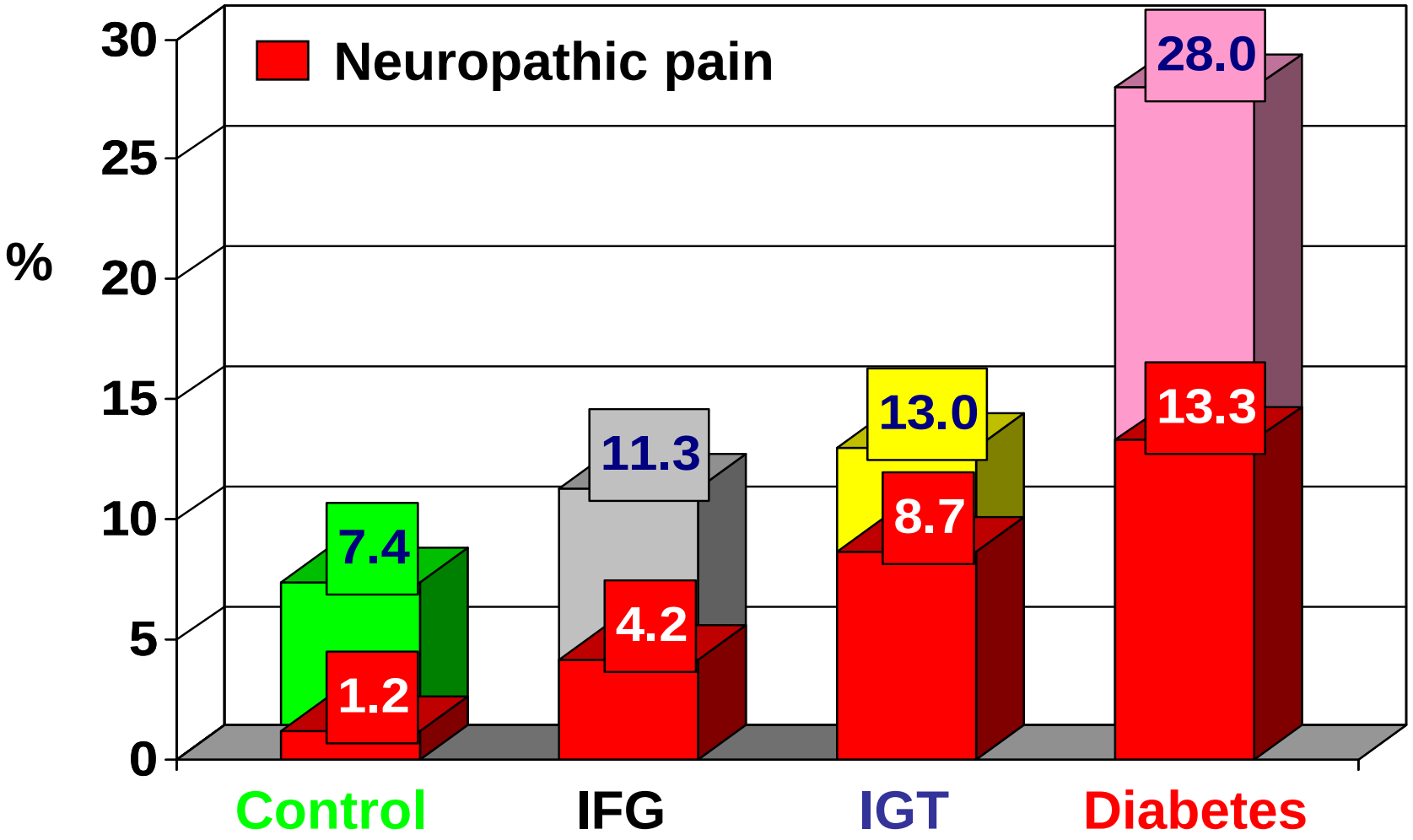
8-year follow-up of polyneuropathy (MNSI >2) after DCCT completion (n=1398)



DCCT, diabetes control and complications trial
MNSI, Michigan neuropathy screening instrument

Martin et al. Diabetes Care, 2006; 29:340
Leroith, Fonseca, Vinik, 2006

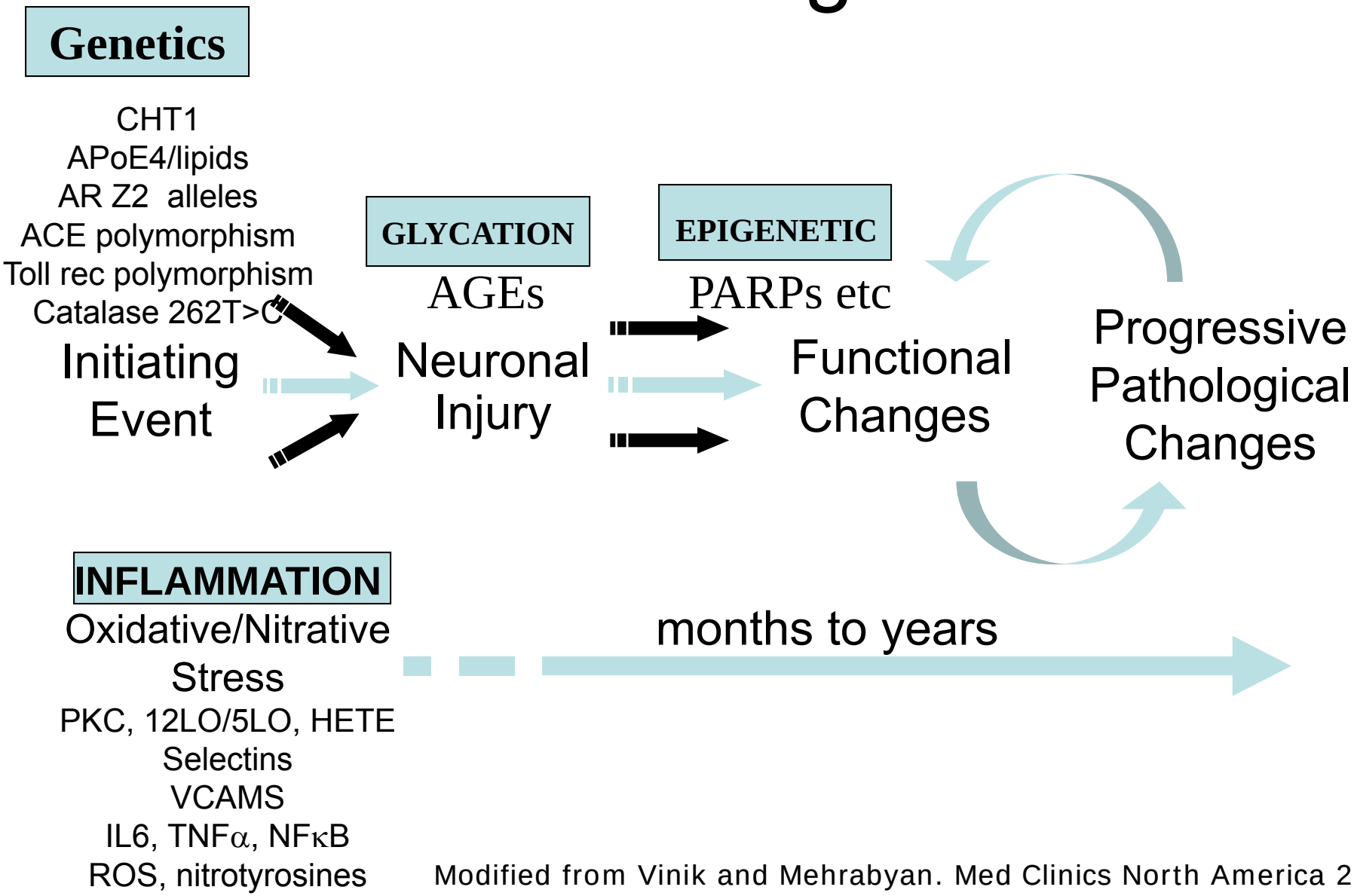
Neuropathy in Prediabetes: Does the Clock Start Ticking Earlier than Diabetes



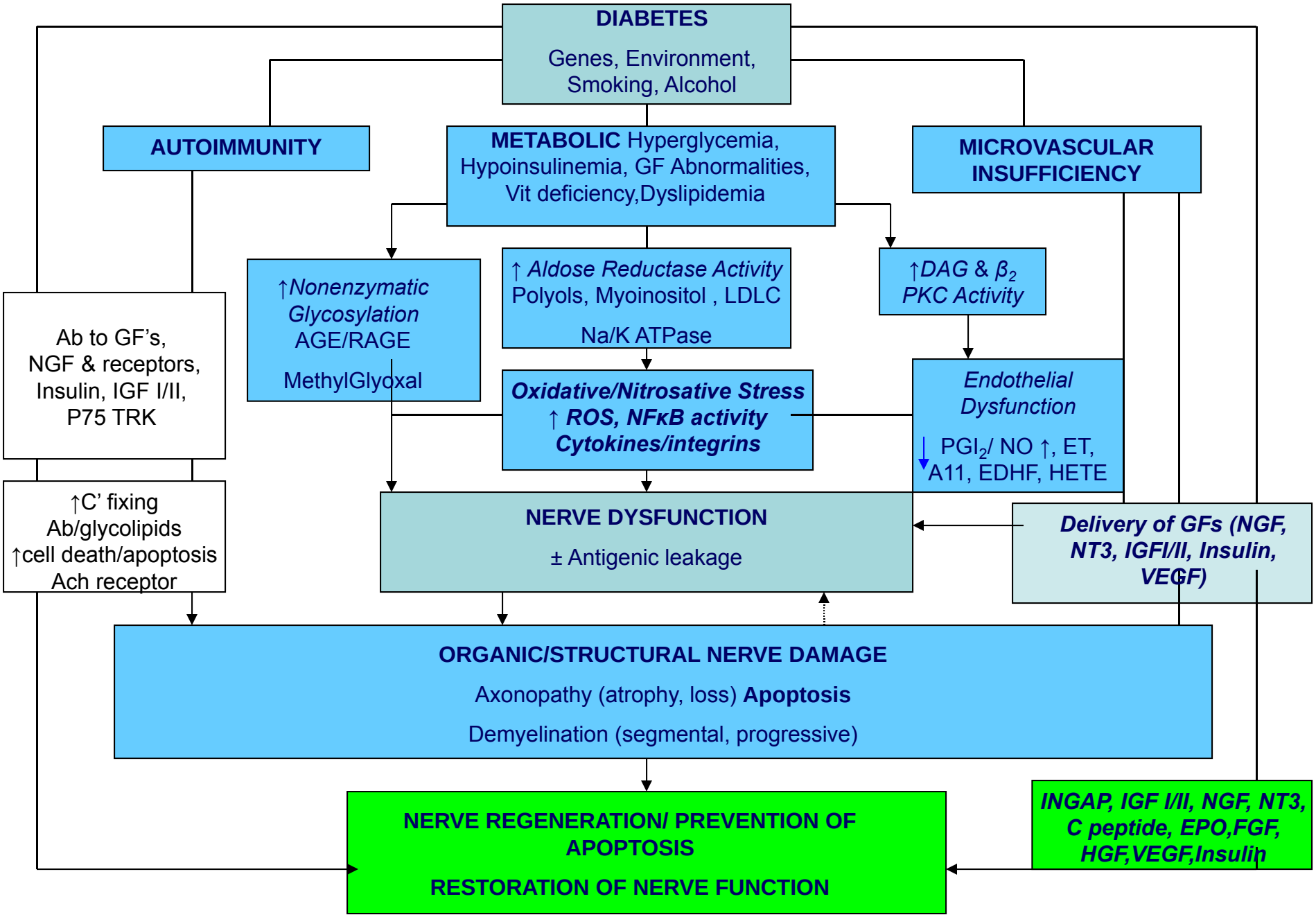
IFG = impaired fasting glucose; IGT = impaired glucose tolerance

Ziegler et al . Papanas, Vinik and Ziegler Nature reviews. Endocrinology 2011;7(11):682-90.

Neuropathy: Disease Initiation/Progression



Modified from Vinik and Mehrabyan. Med Clinics North America 2004



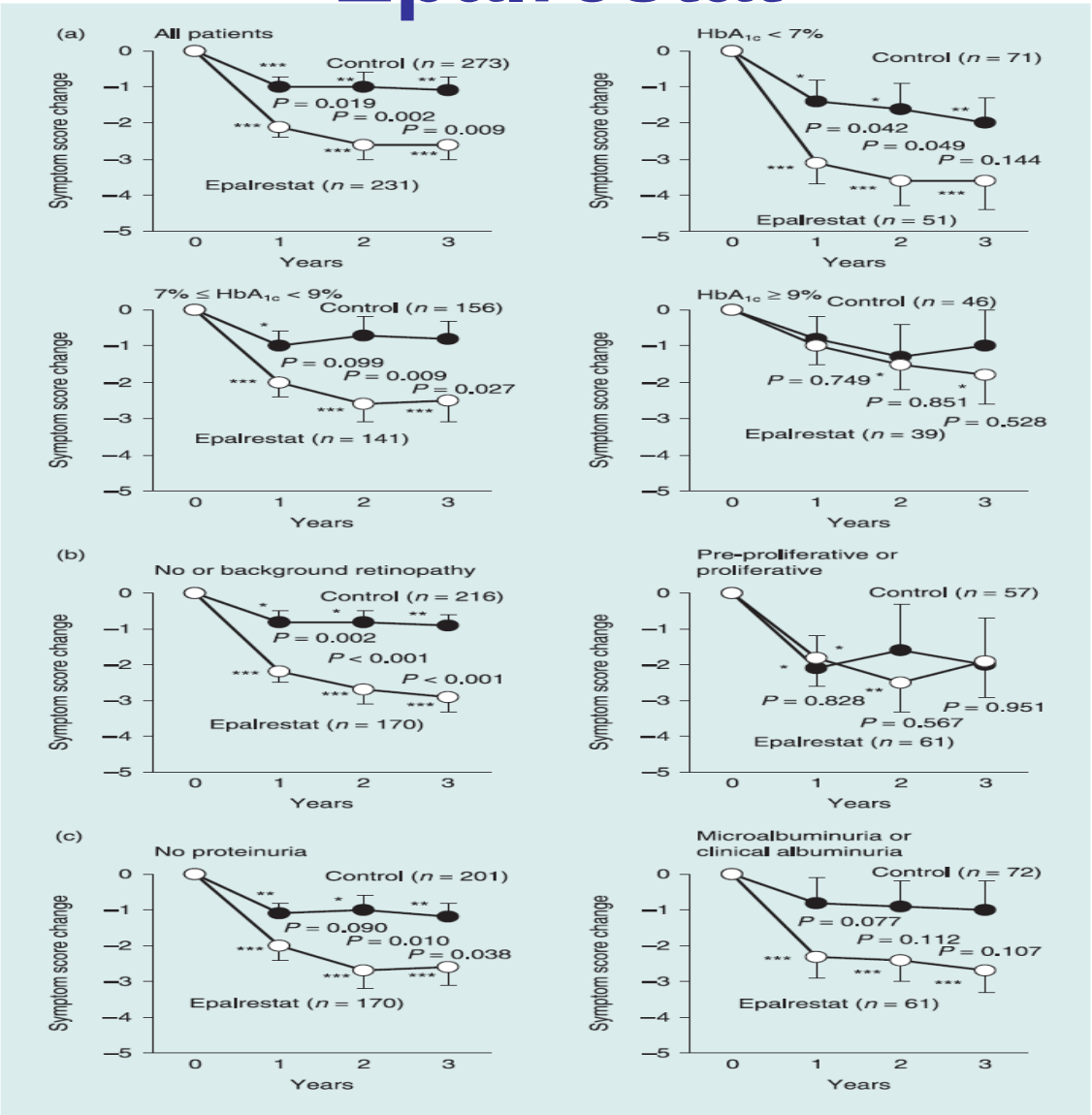
Vinik, Ullal, Casellini Nature Clinical Practice 2(4), 2006, Vinik, Strotmeyer, 2012

Diabetic neuropathy: cellular mechanisms as therapeutic targets

Drug	Proposed mechanism	Preclinical studies	Clinical trial results
Aleglitazar	Dual PPARα/γ agonist	In rats, decreased plasma glucose and LDL cholesterol levels; increased glucose clearance and HDL cholesterol levels; improved insulin resistance[120]	Reduced glycemia in phase II trials; currently in phase III trial for diabetic cardiovascular end points[121]
L-arginine	Improves circulation in microvessels	Produces vasodilation of isolated vessels of all species[122]	No effect on endothelial function or neuropathy score [123]
Zenarestat, epalrestat, ranirestat, fidarestat and five related compounds	Aldose reductase inhibitors	Zenarestat prevented abnormal neurotrophin receptor expression;[124] fidarestat prevented oxidative stress and neuropathy in diabetic rats[125]	Epalrestat is well-tolerated long term[126,127] and approved in Japan;[128] most compounds and pain scores; ranirestat seems to improve motor nerve function in mild to moderate disease;[123] fidarestat showed some adverse effects in long-term treatment[33]
α-Lipoic acid	Antioxidant; pyruvate dehydrogenase activator; other unknown mechanisms	Improved nerve and cardiac disorders in diabetic rats[129]	Approved for standard of care in Germany;[77] some evidence that the compound decreases oxidative stress,[130] prevents AGE formation[131] and improves neuropathic deficits; US trials remain inconclusive[132]
Actovegin	Increases cellular metabolism through an unknown mechanism; increases glucose and oxygen uptake and use; increases ATP turnover	Improved brain metabolic defects in rats with experimental stroke[133]	Sequential intravenous and oral delivery over 160 days improve neuropathic symptoms, vibration perception threshold, sensory function, and quality of life[134]
Fibrates	Lipid lowering	Fenofibrate improves insulin sensitivity[135] and other parameters that affect neuropathy, such as vascularization[136] and lipid metabolism	Clofibrate decreases neuropathy;[138] fenofibrate decreases eye and kidney complications;[138] fenofibrate decreases risk of amputation in patients with diabetes but without macrovascular disease[139]

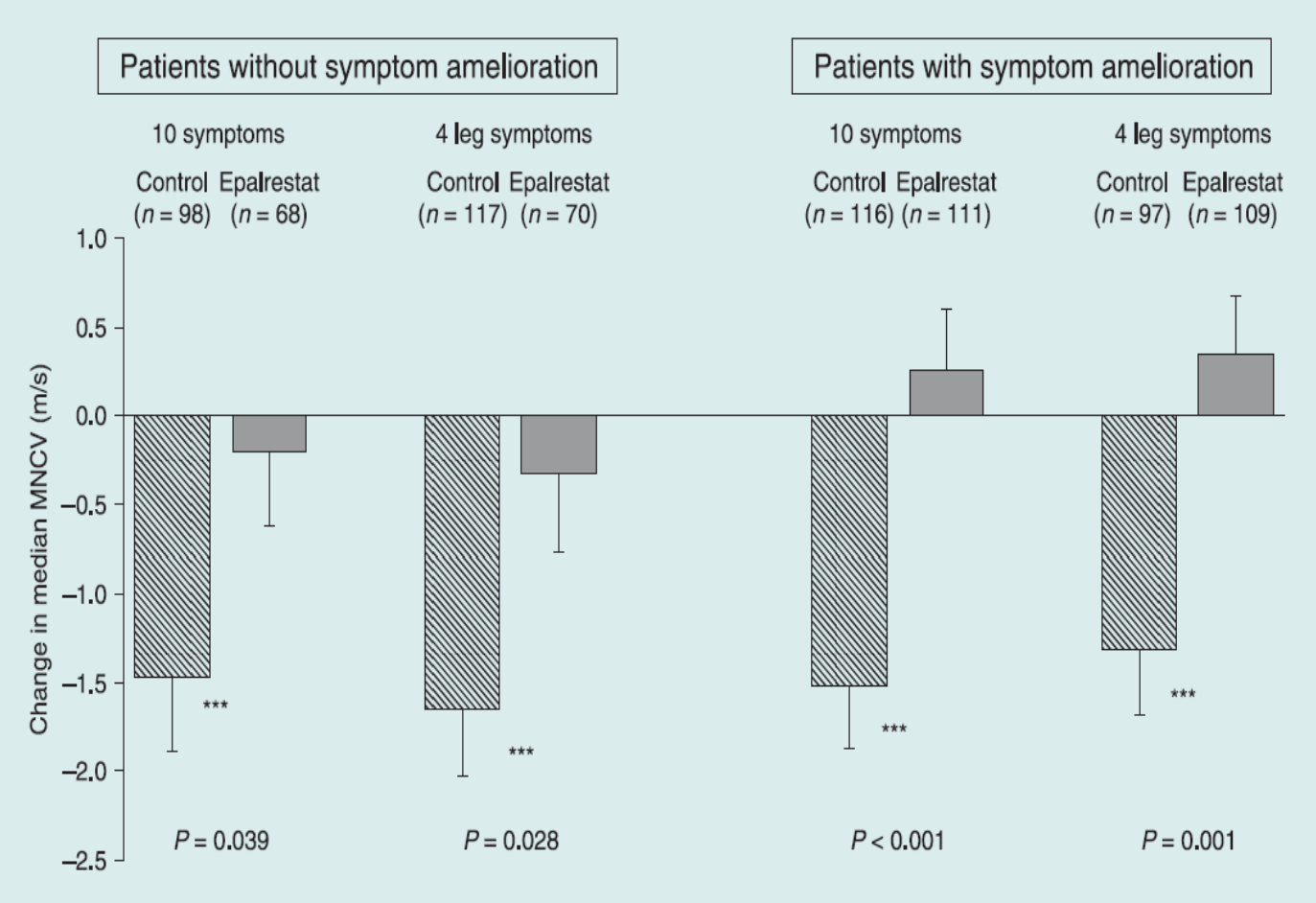
Vincent AM et al. *Nat Rev Neurol* 7:573-583 (2011)

Factors Affecting Responses to Epalrestat



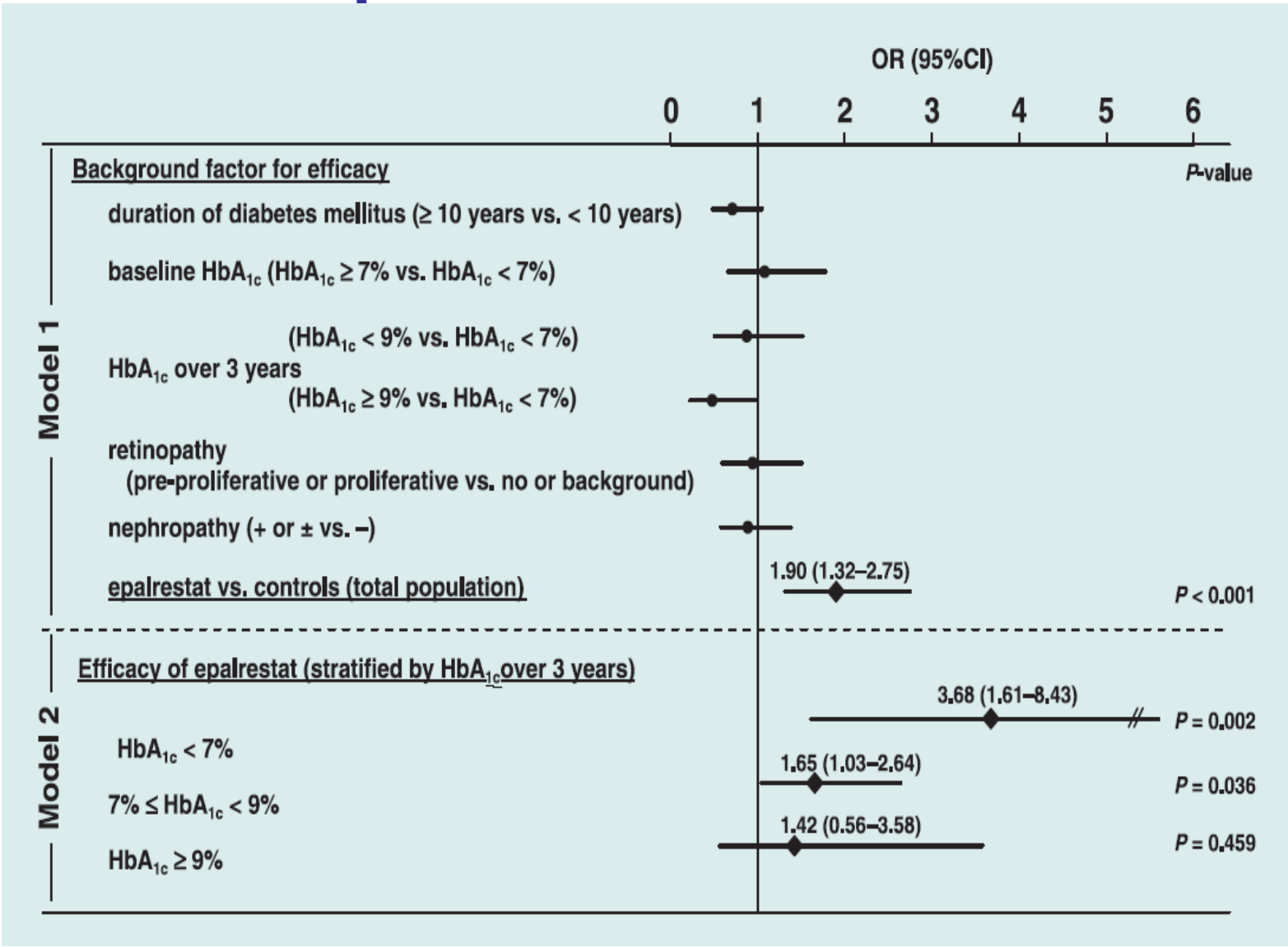
Hotta, N et al. ***Diabetic Medicine***, 25, 818-825, 2008

Amelioration of symptoms and change in median motor nerve conduction velocity (MNCV) after 3 years) of Epalrestat



Hotta, N et al. ***Diabetic Medicine***, 25, 818-825, 2008

Logistic Regression Analysis of the Efficacy of Epalrestat vs. Control



Hotta, N et al. ***Diabetic Medicine***, 25, 818-825, 2008

Diabetic neuropathy: cellular mechanisms as therapeutic targets (Page 2)

Drug	Proposed mechanism	Preclinical studies	Clinical trial results
Gabapentin	GABA analogue that blocks new synapse formation[140]	No preclinical data or known mechanisms; use of anticonvulsants based on similarities between pathophysiology of diabetic neuropathy and epilesy[141]	Blocks pain and improves symptoms of cardiac autonomic neuropathy[142]
Acetyl-L-carnitine	Restoring possibly depleted levels in diabetes; required for mitochondrial function	Improved blood flow and sciatic motor nerve conduction velocity in rats with type 1 diabetes[143]	Early treatment may decrease pain; one of two large studies suggested improvement in NCV and nerve regeneration[144]
Pentoxifylline and pentosan polysulphase	Improves circulation in microvessels by blocking phosphodiesterase; antioxidant	Cliastazol, another phosphodiesterase inhibitor, improved NCV in rats with type 1 diabetes[145] but was ineffective in humans[146]	In combination, these compounds improved cardiovascular autonomic function and vibration perception in type 2 diabetes[147]
Benfotiamine	Blocks AGE formation	Decreased AGE levels and diabetic complications in rats[148,149]	Reviews propose testing in patients, but clinical trials have not been instigated[40,41]
C –peptide	Lacking in type 1 diabetes; binds to a G protein-coupled receptor and alters metabolism[150]	Improved blood flow and early neuropathy in rats with type 1 diabetes[151,152]	Short-term use (<3 months) decreased early evidence of NCV slowing, sensory deficits and autonomic neuropathy in patients with type 1 diabetes[153]
Nerve growth factor	Neurotrophic factor	Decreased neuropathy in rats[154] and mice;[155] however, the endogenous form may be responsible for pain in neuropathy[156]	Some efficacy against sensory deficits, but produced painful adverse effects[157,158]
Ruboxistaurin	Akt inhibitor	Decreased microvascular complications in rodents[159]	Seems to be effective against diabetic retinopathy, but no effect on neuropathy in phase III trials[160]
Basic fibroblast growth factor	Stimulates angiogenesis and nerve cell regeneration	Intravenous administration in rats modestly improves blood flow, NCV deficits and hypoalgesia[161]	Not determined

Abbreviations: AGE, advanced glycation end product; GABA, γ-aminobutyric acid; NCV, nerve conduction velocity; PPAR, peroxisome proliferator-activated receptor

Vincent AM et al. *Nat Rev Neurol* 7:573-583 (2011)

Reviews/Commentaries/ADA Statements
REVIEW ARTICLE

Diabetic Neuropathies: Update on Definitions, Diagnostic Criteria, Estimation of Severity, and Treatments

"The antioxidant α-lipoic acid administered i.v. is the only pathogenetic treatment that has efficacy confirmed from several randomized controlled trials and confirmation in a meta-analysis (level A evidence)."

Tesfaye, Vinik et al., Diabetes Care 2010; 33: 2285–2293

Efficacy of Alpha Lipoic Acid in the NATHAN 4y Trial

Study Design and Results

- 460 patients with mild to moderate DSPN ,
- DBPC multicenter trial
- Failed to meet primary endpoint NISLL + 7
- Improved NIS (p0.028), NIS-LL (p=0.05) and more responded (NIS (p=0.013) and NISLL (p=0.025)
- Nerve conduction and QST did not deteriorate in placebo

Conclusions

- The first and longest trial in DSPN
- Four year treatment with ALA failed to achieve primary endpoint
- Clinically meaningful improvements and arrest of progression of neuropathy impairment
- Because primary endpoints did not deteriorate in placebo secondary prevention not possible

Ziegler et al Diabetes Care 2011; 34: 2054-2060.

The Ideal Endpoint . . .

- Relevant to the disease and the population under investigation – correlates with “clinically meaningful” symptoms/signs/outcomes.
  - *Direct assessment of axon number and function*
- Reproducibl
- Respon
- *Biolog*
- Accep munity, regulato jects.

Can we fulfill all of the above?

Neuropathy Impairment Score

- **Most widely used quantitative assessment in diabetic polyneuropathy**
- **Lower Limb only (NIS-LL) (score 0-88)**
- **Components tested**
  - Muscle Power (0-64)
  - Sensation (0-16)
  - Reflexes (0-8)
- **Correlates with disease severity in DPN**
  - NIS-LL increases by 0.9 points/year in DPN
  - NIS-LL increase of 2 points clinically significant*

Summated (Σ) Scores of Neurophysiologic Function

Σ7 – Primarily Large Fiber

- Vibration detection threshold
- Heart rate variability with deep respiration
- Nerve conduction studies
  - Peroneal
  - Tibial nerve
  - Sural nerve

Σ3 Small fiber function

- Cooling detection threshold
- Heat pain threshold
- Heart rate variability with deep respiration

Dyck 1987; Dyck 1997; Dyck 2005; Kim 2009

Challenges in Design of Multicenter Trials in DPN

Comparison of outcomes in:

- Rochester observational study
- Viatris (Alpha Lipoic Acid) trial
- Ruboxistaurin trial

***Diabetes Care* 30:2619–2625, 2007**

Reproducibility of neuropathic end point measurements at onset of Viatris and Lilly controlled clinical trials of DSPN

	ICC			
	Viatris		Lilly	
	First and second exam	First and third exam	First and second exam	First and third exam
Ankle reflexes (0–4 pts)	0.82	0.80	—	0.83
Great toe vibration (0–4 pts)	0.77	0.73	—	0.88
NIS(LL) (pts)	0.82	0.82	—	0.89
NSC(LL) severity (pts)	—	0.80	—	0.81
Σ DCCT criteria (0–12 pts)	—	0.77	—	0.88
Peroneal motor CV nd	0.85	0.85	0.84	0.80
Tibial motor DL nd	0.66	0.53	0.66	0.70
Sural SNAP nd	0.91	0.87	0.69	0.65
Σ 5 NC tests nd	0.84	0.82	0.78	0.80
VDT nd	0.73	0.76	0.67	0.58
CDT nd	0.86	0.86	—	—
HP:5 nd	0.84	0.83	—	—
Σ 3 QST tests nd	0.85	0.85	—	—
HRDB nd	0.81	0.83	0.72	0.73

Abbreviations are given in Table 1. Additional abbreviations: CDT, cooling detection threshold using CASE IV; HP:5, heat pain 5, severity of the pain experience from 1 (least) to 10 (most).

***Dyck et al Diabetes Care* 30:2619–2625, 2007**

Median regression slopes ($\bar{b}$) of NIS (LL) ≥ 2 points over time in the Rochester, Viatris, and Lilly cohorts using different criteria for the diagnosis of polyneuropathy

Cohort	Rochester $\bar{b}$ per 4 years	Rochester *P**	Viatris $\bar{b}$ per 4 years	Viatris *P*	Lilly $\bar{b}$ per year	Lilly *P*
Entry criteria	NIS(LL) ≥2 points					
Number of patients (mode)	83		191		234	
Ankle reflexes† (0–4 pts)	−0.35	0.02	−0.27	<0.01	0.24	0.73
Great toe vibration† (0–4 pts)	0.40	<0.01	0.12	0.30	−0.25	<0.01
NIS(LL)† (pts)	0.82	0.99	0.16	0.81	0.35	0.02
NSC(LL) severity† (pts)	−0.13	0.29	−0.52	0.23	−3.27	<0.01
Σ DCCT criteria† (0–12 pts)	−0.21	0.21	−0.27	0.10	−0.38	<0.01
Peroneal motor CV nd	0.08	0.33	−0.00	0.54	0.05	0.05
Tibial motor DL nd	−0.11	0.27	−0.10	0.09	−0.04	0.10
Sural SNAP nd	0.23	<0.01	+0.00	0.05	0.14	<0.01
Σ 5 NC tests nd	−0.20	0.44	−0.21	0.05	0.29	0.05
VDT (CASE IV) nd	0.53	0.02	+0.00	0.34	−0.40	<0.01
Σ 3 QST nd	2.48	<0.01	−0.28	0.02		
HRDB nd	+0.00	0.67	0.05	0.55	0.10	0.13

***Dyck et al Diabetes Care* 30:2619–2625, 2007**

Median regression slopes ($\bar{b}$) of Σ 5 NC tests nd ≥ 95th over time in the Rochester, Viatris, and Lilly cohorts using different criteria for the diagnosis of polyneuropathy

	Rochester		Viatris		Lilly	
Cohort	$\bar{b}$ per 4 years	*P**	$\bar{b}$ per 4 years	*P*	$\bar{b}$ per year	*P*
Entry criteria	Σ 5 NC tests nd ≥95th					
Number of patients (mode)	108		191		130	
Ankle reflexes† (0–4 pts)	−0.10	0.28	−0.27	<0.01	−1.22	0.07
Great toe vibration† (0–4 pts)	0.38	<0.01	0.12	0.30	−0.08	0.42
NIS(LL)† (pts)	1.04	0.03	0.16	0.81	−1.42	0.07
NSC(LL) severity† (pts)	0.05	0.78	−0.52	0.23	−2.38	<0.01
Σ DCCT criteria† (0–12 pts)	0.17	0.28	−0.27	0.10	−1.73	<0.01
Peroneal motor CV nd	0.14	0.83	−0.00	0.54	+0.00	0.82
Tibial motor DL nd	−0.38	<0.01	−0.10	0.09	−0.07	0.05
Sural SNAP nd	0.11	0.03	+0.00	0.05	0.11	0.03
Σ 5 NC tests nd	−0.52	0.08	−0.21	0.05	−0.37	0.26
VDT (CASE IV) nd	0.38	0.01	+0.00	0.34	−0.52	<0.01
Σ 3 QST nd	2.10	<0.01	−0.28	0.02		
HRDB nd	+0.00	0.66	0.05	0.55	0.04	0.50

***Dyck et al Diabetes Care* 30:2619–2625, 2007**

Median regression slopes ($\bar{b}$) of DCCT ≥ 2 of 3 criteria over time in the Rochester, Viatris, and Lilly cohorts using different criteria for the diagnosis of polyneuropathy

	Rochester		Viatris		Lilly	
Cohort	$\bar{b}$ per 4 years	*P**	$\bar{b}$ per 4 years	*P*	$\bar{b}$ per year	*P*
Entry criteria	DCCT ≥2 of 3 criteria					
Number of patients (mode)	30		187		222	
Ankle reflexes† (0–4 pts)	−0.11	0.97	−0.28	<0.01	0.26	0.73
Great toe vibration† (0–4 pts)	−0.07	0.90	0.10	0.37	−0.27	<0.01
NIS(LL)† (pts)	0.90	0.48	0.04	0.89	0.63	0.04
NSC(LL) severity† (pts)	−0.28	0.15	−0.55	0.21	−3.35	<0.01
Σ DCCT criteria† (0–12 pts)	−0.54	0.21	−0.31	0.07	−0.39	<0.01
Peroneal motor CV nd	0.94	0.56	−0.00	0.51	0.05	0.05
Tibial motor DL nd	−0.09	0.59	−0.09	0.12	−0.05	0.05
Sural SNAP nd	0.10	0.34	+0.00	0.05	0.12	<0.01
Σ 5 NC tests nd	0.05	0.57	−0.16	0.07	0.28	0.09
VDT (CASE IV) nd	0.52	0.12	+0.00	0.36	−0.38	<0.01
Σ 3 QST nd	2.14	0.01	−0.28	0.02		
HRDB nd	−0.00	0.98	0.05	0.50	0.08	0.14

The Plague of the Placebo

- Using “drop in” drugs
- Progression of small fiber changes vs. static changes in large fiber function.
  - The multicenter Ruboxistaurin Trial

Patient baseline characteristics

Characteristic	Placebo
n	262
Female sex	147 (56.1)
Type 1 diabetes	68 (26.0)
Age (years)	48.1 ± 9.4
Caucasian	207 (79.0)
BMI (kg/m^2)	30.0 ± 6.5
A1C (%)	7.6 ± 1.4
Used insulin	159 (60.7)
Duration of diabetes (years)	11.4 ± 9.2
Duration of neuropathy (years)	2.7 ± 2.8
Statin medication use	68 (26.0)
Chronic symptom medication use	38 (14.5)
Antihypertensive medication use	157 (59.9)
ACE inhibitor or ARB use	131 (50.0)

Tesfaye, S et al., ***Diabetes Care*** 30:2626-2632, 2007

Baseline to end point change at 1 year in placebo-administered patients

Characteristic	Baseline	Baseline to end point improvement	*P* value*
NTSS-6 total score (points)	9.76 ± 3.8	3.73 ± 3.8	<0.001
NIS[LL] (points)	6.95 ± 5.0	0.63 ± 3.4	0.005
Quantitative sensory testing (JND units)	20.43 ± 2.1	0.42 ± 2.1	0.003
		Baseline to end point worsening	
HRDB (inspiration – expiration) (beats/min)	11.92 ± 6.7	0.78 ± 3.9	0.003
Peroneal NCV (m/s)	43.05 ± 4.9	0.38 ± 2.2	0.012
Tibial F-wave latency (ms)	54.93 ±6.1	0.33 ± 2.4	0.045
Sural amplitude (μV)	9.10 ± 5.3	1.12 ± 3.7	<0.001
Sural peak latency (ms)	3.95 ±0.49	0.058 ± 0.37	0.021
A1C (%)	7.58 ± 1.4	0.28 ± 1.2	*P* <0.001

Tesfaye, S et al., ***Diabetes Care*** 30:2626-2632, 2007

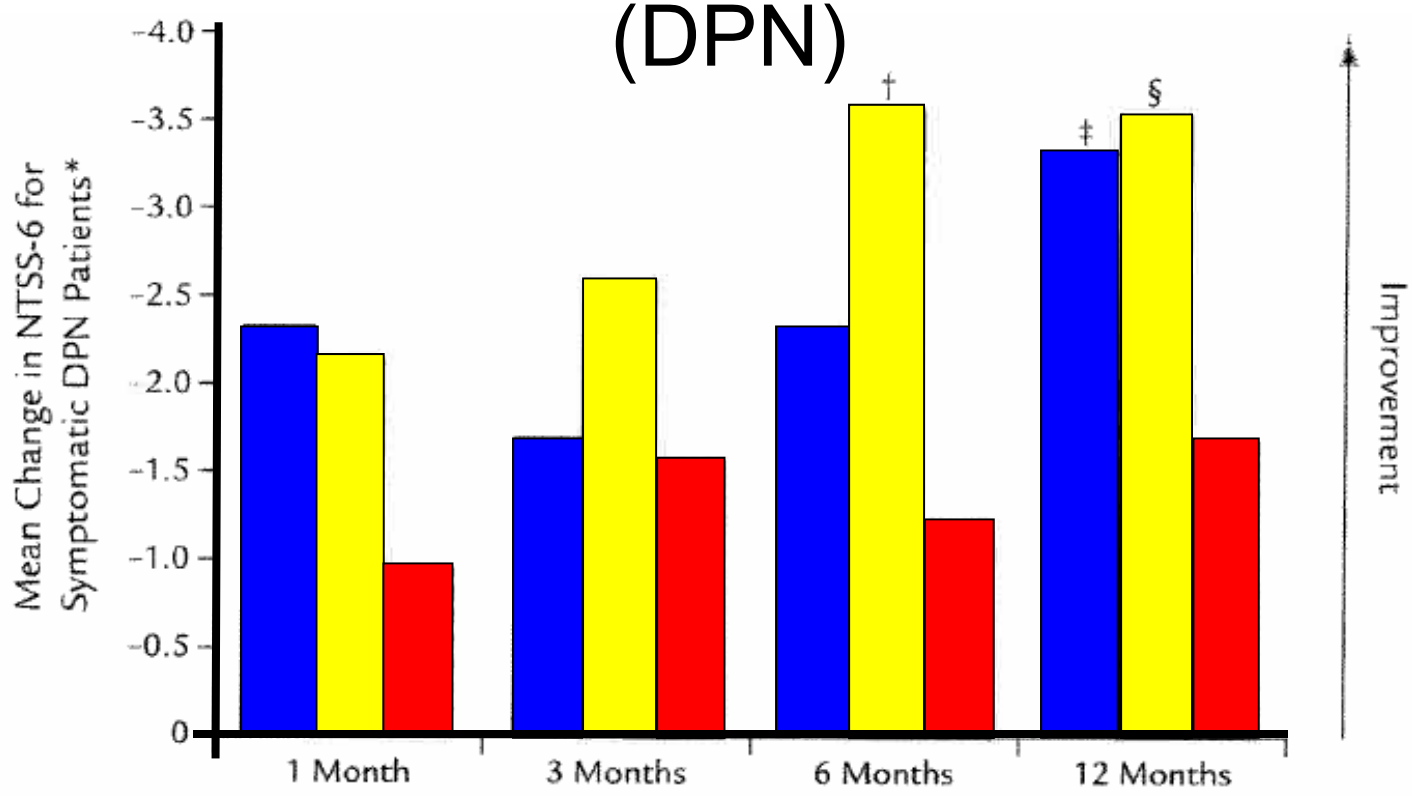
Patient characteristics that impact clinically significant improvement in neuropathic symptoms

Characteristic	Symptom improvement ≥ 50%	No symptom improvement <50%	*P* value
Baseline NTSS-6 total score (points)	9.17 ± 2.87	10.19 ± 3.58	0.0168
Baseline NIS[LL] (points)	6.45 ± 4.25	7.31 ± 5.41	0.1714
NIS[LL] changes from baseline (points)	-1.21 ± 3.37	-0.21 ± 3.41	0.0277
Baseline NIS[LL] + 7 (points)	13.28 ± 5.99	15.26 ± 7.17	0.0219
NIS[LL]+7 change from baseline (points)	0.027 ± 7.7	2.51 ± 12. 7	0.0969
Baseline VDT (JND units)	20.00 ± 2.06	20.71 ± 2.07	0.0087
VDT change from baseline (JND units)	-0.582 ± 2.39	-0.304 ± 1.87	0.3228
Baseline peroneal NCV (m/s)	43.34 ± 4.96	42.85 ± 4.90	0.4273
Peroneal NCV change from baseline (m/s)	0.015 ± 2.32	-0.674 ± 2.15	0.0260
Baseline tibial F-wave latency (ms)	54.54 ± 6.19	55.20 ± 6.06	0.3939
Tibial F-wave latency change from baseline (ms)	0.285 ± 2.66	0.362 ± 2.21	0.8165
Baseline sural amplitude (μV)	10.19 ± 5.44	8.34 ± 5.13	0.0076
Sural amplitude change from baseline (μV)	-1.23 ± 3.55	-1.04 ± 3.76	0.6985
Age (years)	46.30 ± 9.15	49.28 ± 9.36	0.0128
Baseline BMI (mg/kg^2)	29.07 ± 7.14	30.67 ± 5.95	0.0528
Baseline SBP (mmHg)	124.22 ± 14.21	128.26 ± 15.68	0.0361
Type 1 diabetes	33 (31.1)	34 (21.9)	0.0962
Baseline chronic symptom medication use	9 (8.5)	29 (18.7)	0.0248
Baseline antihypertensive medication use	56 (52.8)	101 (65.2)	0.0464
Baseline statin use	21 (19.8)	47 (30.3)	0.0591

Tesfaye, S et al., ***Diabetes Care*** 30:2626-2632, 2007

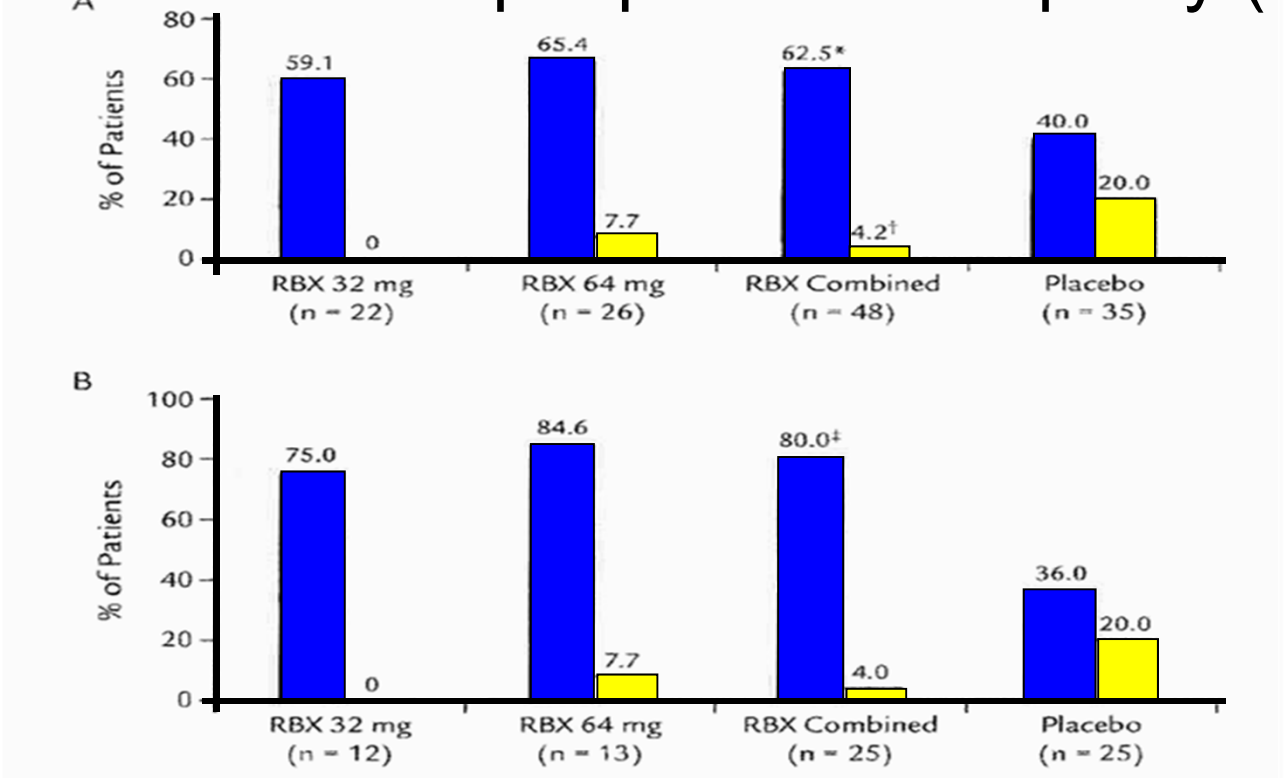
Translating Phase 2 to Phase 3 and from Single to Multicenter Trials

The effect of ruboxistaurin (RBX) mesylate on the Neuropathy Total Symptom Score-6 (NTSS-6) total score in 83 patients with symptomatic diabetic peripheral neuropathy (DPN)



*Negative change indicates improvement; †p=0.012 versus placebo; ‡p=NS versus placebo; §p=0.015 versus placebo.

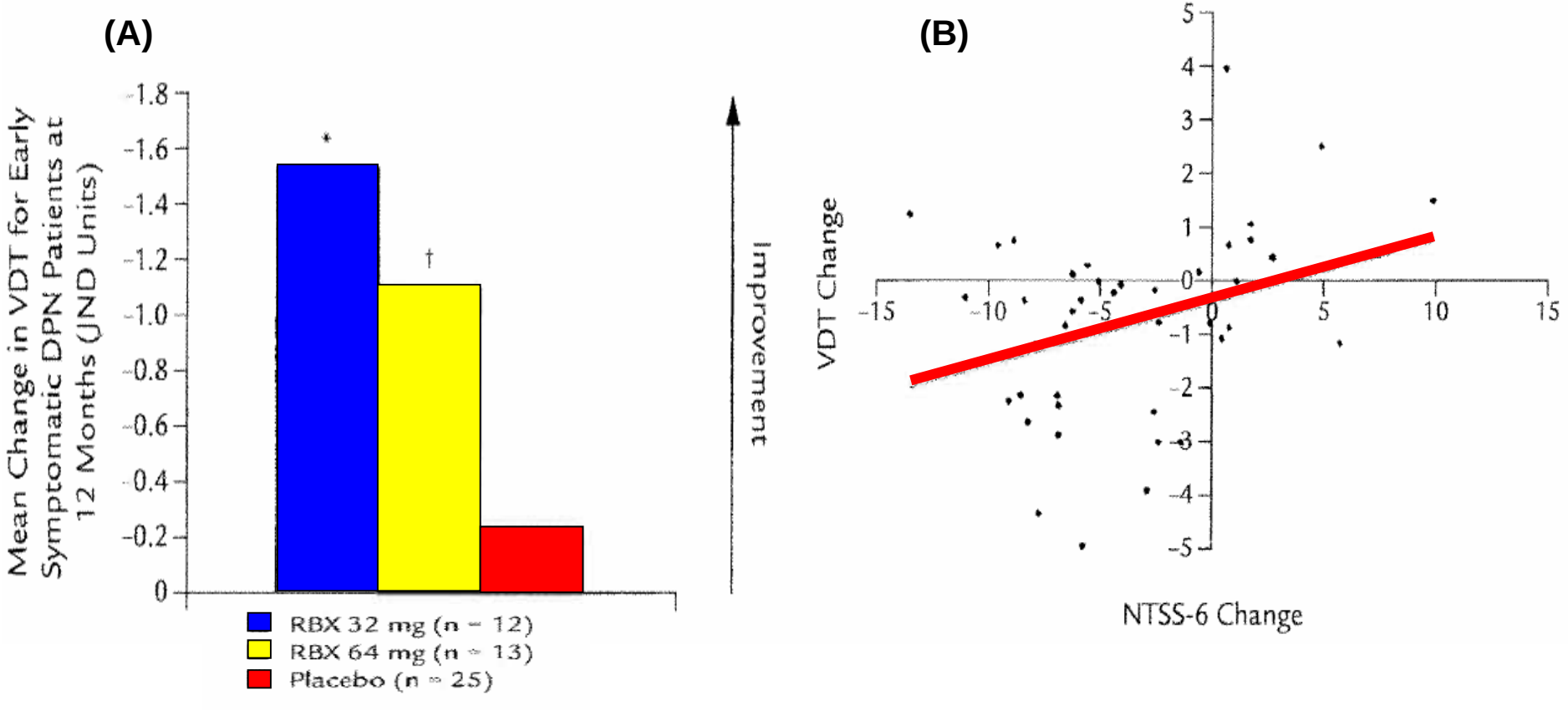
The effect of ruboxistaurin (RBX) mesylate on the change in Neuropathy Total Symptom Score-6 (NTSS-6) total score for patients with less severe and symptomatic diabetic peripheral neuropathy (DPN)



Clinically significant improvement was defined as NTSS-6 score reductions ≥2.
(A) Symptomatic DPN patients (ie, NTSS-6 total score >6; 83 of 205 patients).
(B) Patients with mild, early symptomatic DPN (ie, NTSS-6 total score >6, detectable sural sensory nerve action potential; 50 of 205 patients).

*p=0.049 versus placebo; †p=0.032 versus placebo; ‡p=0.004 versus placebo.

The effect of ruboxistaurin (RBX) mesylate on vibration detection threshold (VDT)

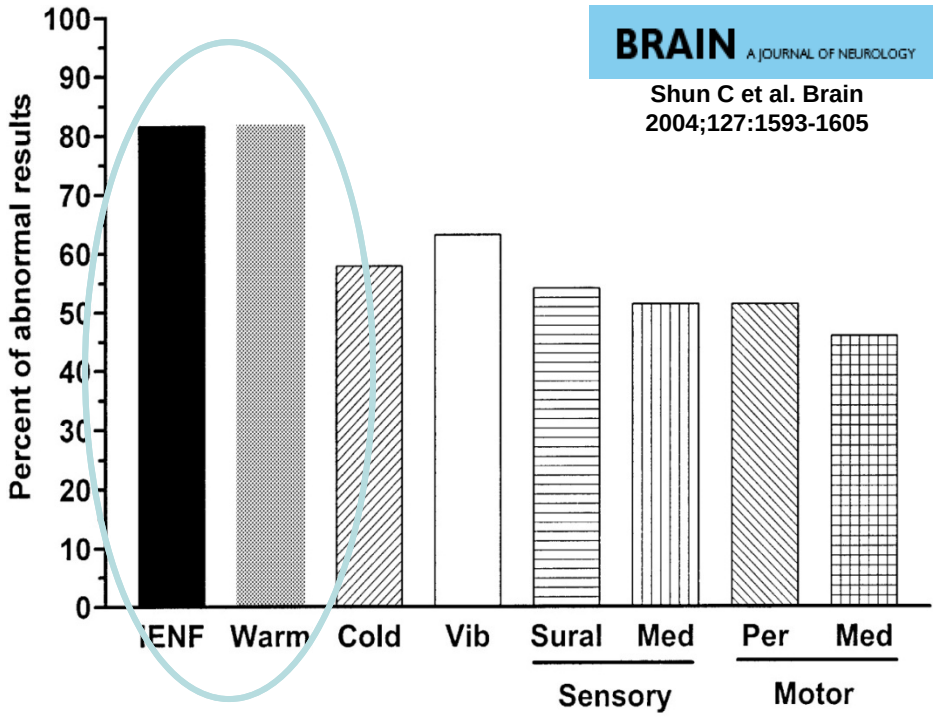


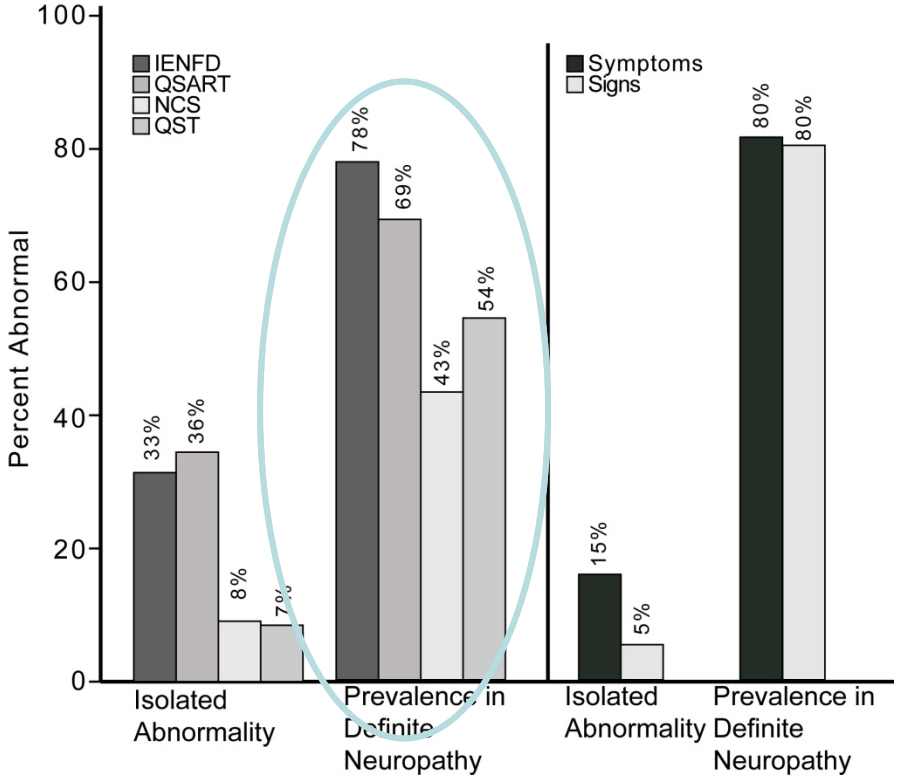
(A) Patients with mild, early symptomatic diabetic peripheral neuropathy (DPN) (ie, detectable sural sensory nerve action potential; 50 of 205 patients).

(B) Correlation between change in Neuropathy Total Symptom Score-6 (NTSS-6) total score and the change in VDT (r=0.322, p=0.033; 50 of 205 patients).

JND = just noticeable difference; *p=0.012 versus placebo; †p=0.026 versus placebo.

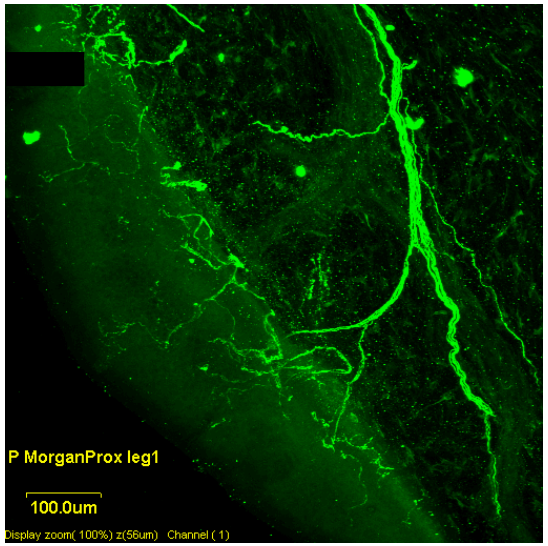
Small fiber measures have greater diagnostic sensitivity



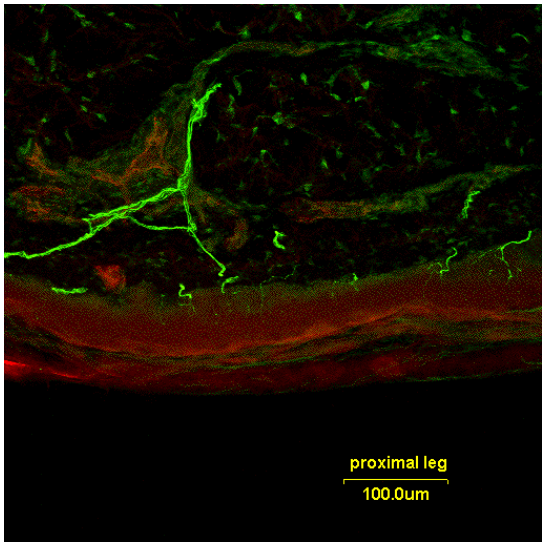


IENF Loss in Small Fiber Neuropathy

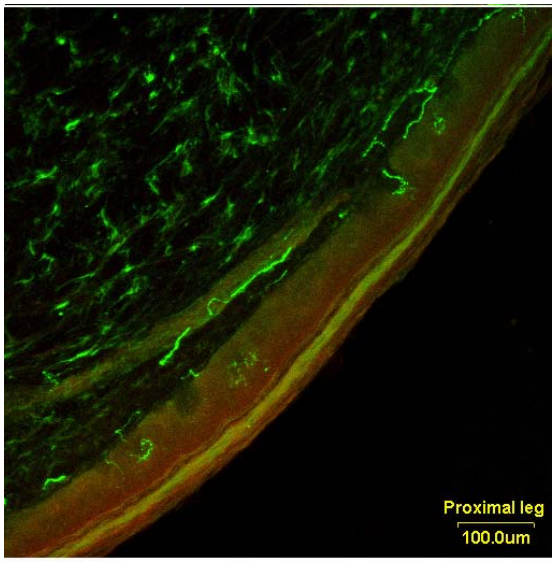
Control



Metabolic Syndrome

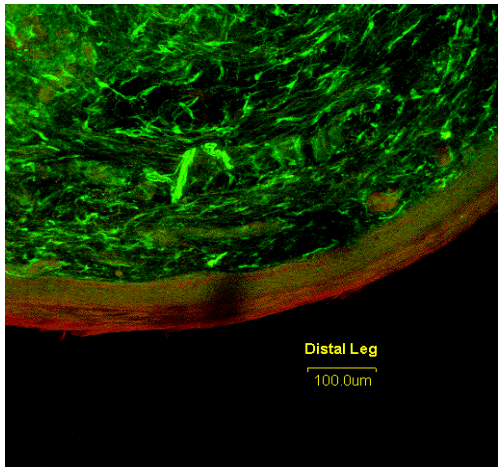


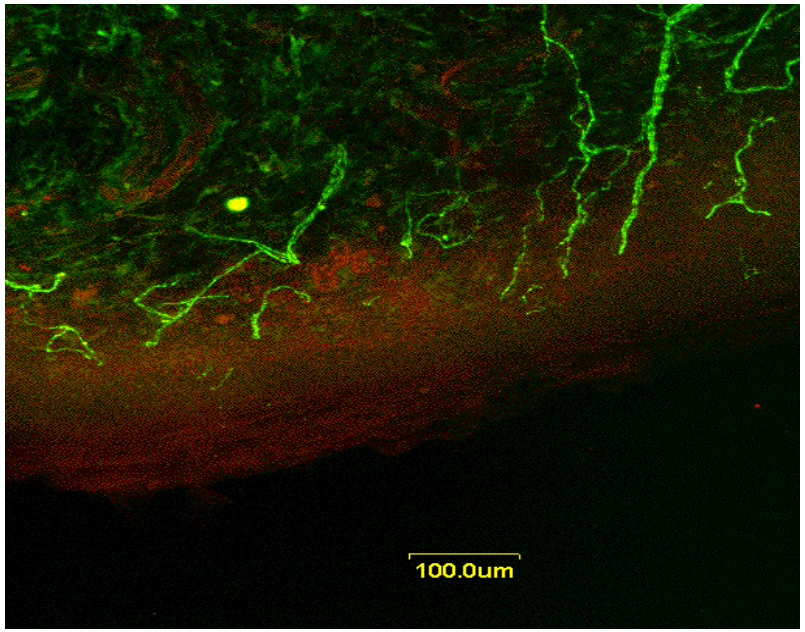
Diabetes



Vinik AI, et al. *Nature Clinical Practice Endocrinol Metab*. 2006;2:269-281.
Pittenger, Burcus, McNulty, Basta, Vinik. Diabetes Care 27:1974-79, 2004;
Pittenger,Mehrabyan, Simmons, Rice, Dublin, Barlow,Vinik, Metab. Syndrome 3:113-121, 2005

Small Fibers have Greater Plasticity and Regrow Upon Stimulation





Before Topiramate **After Topiramate**

Boyd, Barlow, Pittenger, Simmons, Vinik
Diabetes, Metabolic Syndrome and Obesity 2010

Improvement in Endpoints in Ruboxistaurin and Topiramate Treated Subjects

QOL Domain	Placebo		RBX		TPX	
	Difference	p-value	Difference	p-value	Difference	p-value
Total QOL	-5.56±3.49	NS	-9.56±-4.13	<0.04	-12.22±2.76	<0.001
Symptoms	-0.28+/-0.82	NS	-2.27+/-0.81-	<0.004	-4.89+/0.88	<0.0001
Large Fiber	-3.67+/-2.23	NS	-4.74+/-2.69	NS	-5.61+/-1.64	<0.05
Small Fiber	-1.22+/-0.69	NS	-0.5+/-0.36	NS	-1.06+/-0.56	NS
ADL	-0.39+/-0.50	NS	-1.06+/-0.62	NS	-0.61+/-0.54	NS
Autonomic	0+/-0.29	NS	-0.56+/-0.38	NS	-0.06+/-0.26	NS

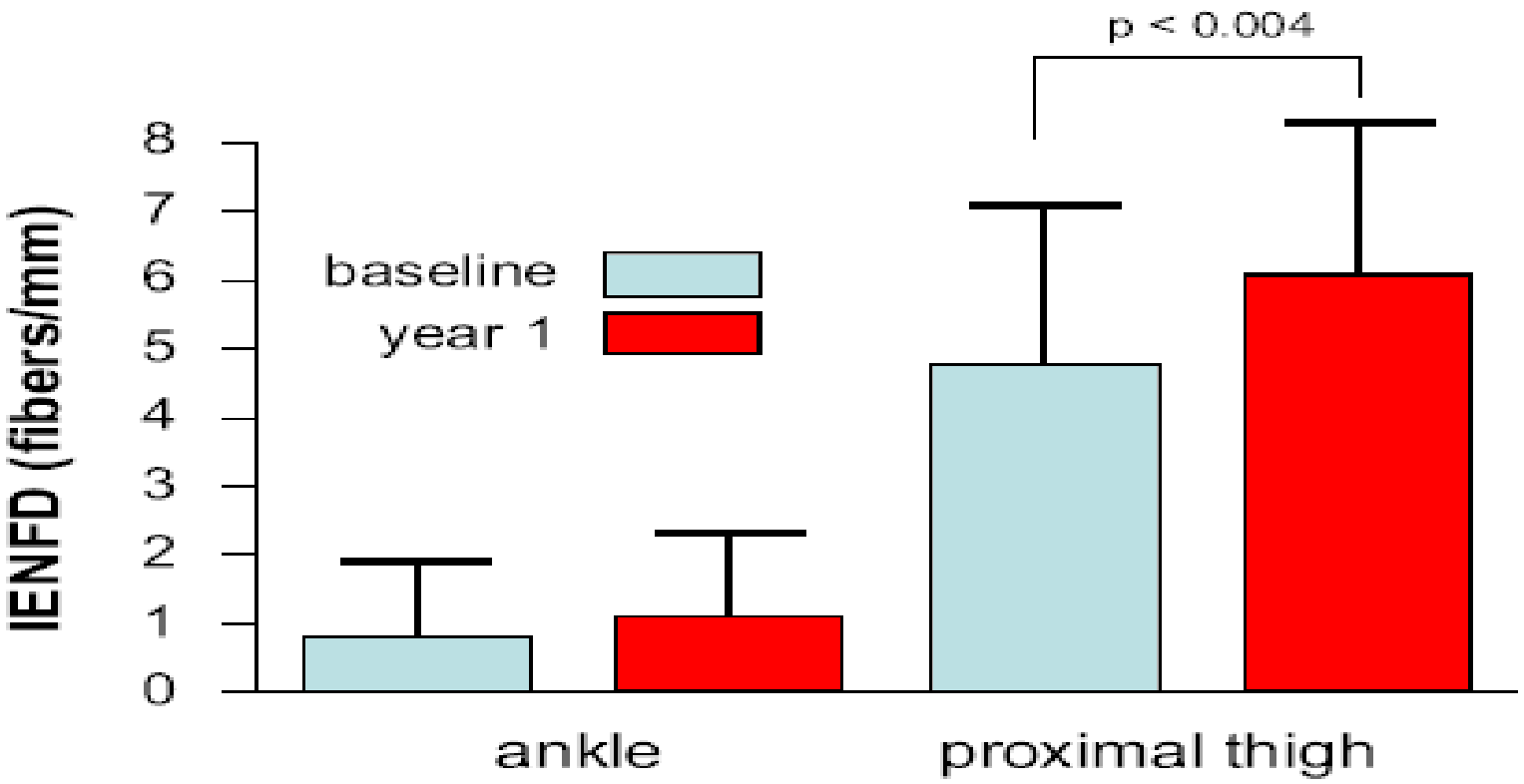
Data is presented as mean (± SEM). Abbreviations: ADL, activities of daily living; QOL, Quality of life; RBX, ruboxistaurin; TPX, topiramate

Boyd, Casellini, Vinik, and Vinik. J Sci and Technology, 5: 714-722, 2011

Effects of Topiramate on Metabolic Parameters and Cognitive Function

Variable	Baseline (Pre)	18 Weeks (Post)	Significance
Weight	**228 ± 11.9**	**220 ± 12.3**	**p<.0001**
BMI	**32.5 ± 1.2**	**31.3 ± 1.3**	**p< .001**
Diastolic BP	**81 ± 1.9**	**71 ± 1.6**	**p <.0001**
Systolic BP	**143± 4.1**	**122 ± 3.1**	**p<.0001**
HBA1c	**7.4 ± 0.31**	**6.8 ± 0.20**	**p<.0001**
Total Neuropathy Score	**31.1 ± 15.5**	**21.0 ± 11.5**	**p= 0.0026**
Touch Threshold	**2.7 ± 3.1**	**.45 ± 1.4**	**P=0.004**
Prickling Threshold	**4.3 ± 2.1**	**2.15 ± 2.43**	**P=0.0008**
Vibration Threshold	**5.4± 2.3**	**4.4± 2.2**	**P=0.039**

Lifestyle Intervention for Pre-Diabetic Neuropathy



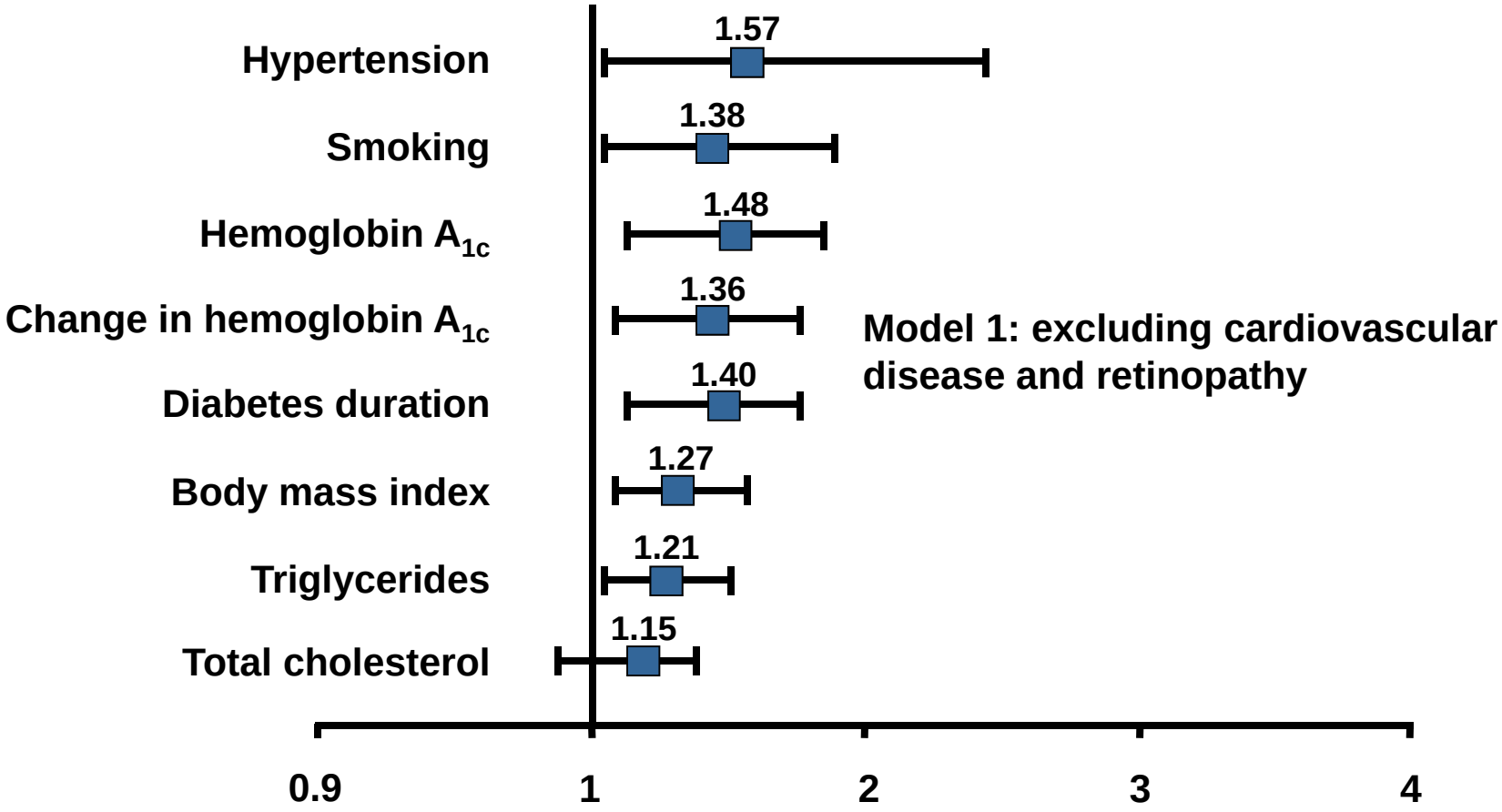
Smith and Singleton. The Neurologist 2008;14: 23–29)

Noninvasive Tests of Small Fiber Function

- Laser Doppler Flare or Blood Flow
- Corneal Confocal Microscopy
- Contact Heat or Laser Heat Evoked Potentials
- Sudorimetry
  - QSART
  - Sudoscan
- Quantitative Autonomic Function Tests

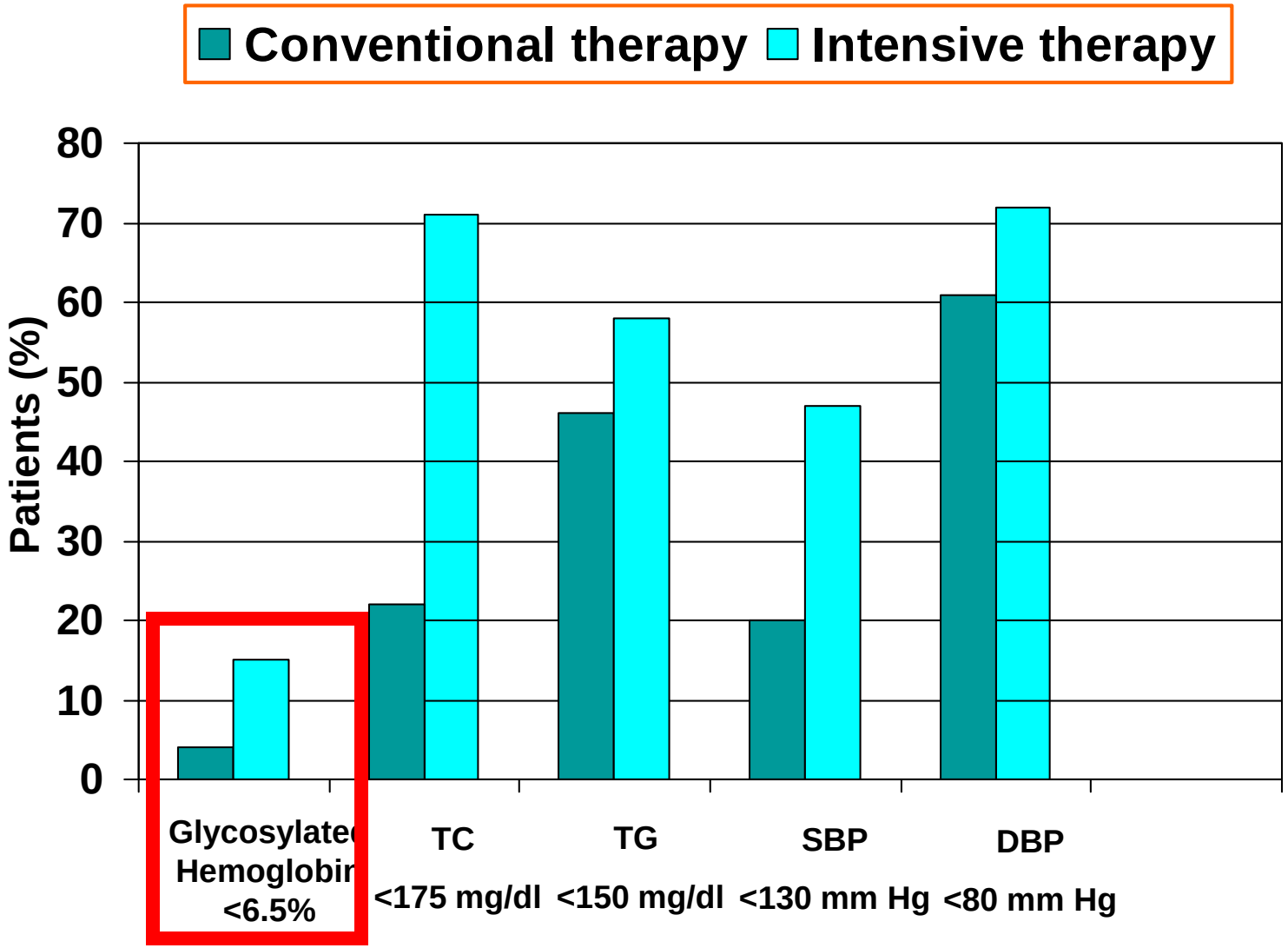
EURODIAB: Risk Factors for Incidence of Polyneuropathy

Odds ratios (95% CI); n = 1101 with type 1 diabetes; follow-up 7.3 ± 0.6 years



Tesfaye S, et al. *N Engl J Med*. 2005;352:341-350.

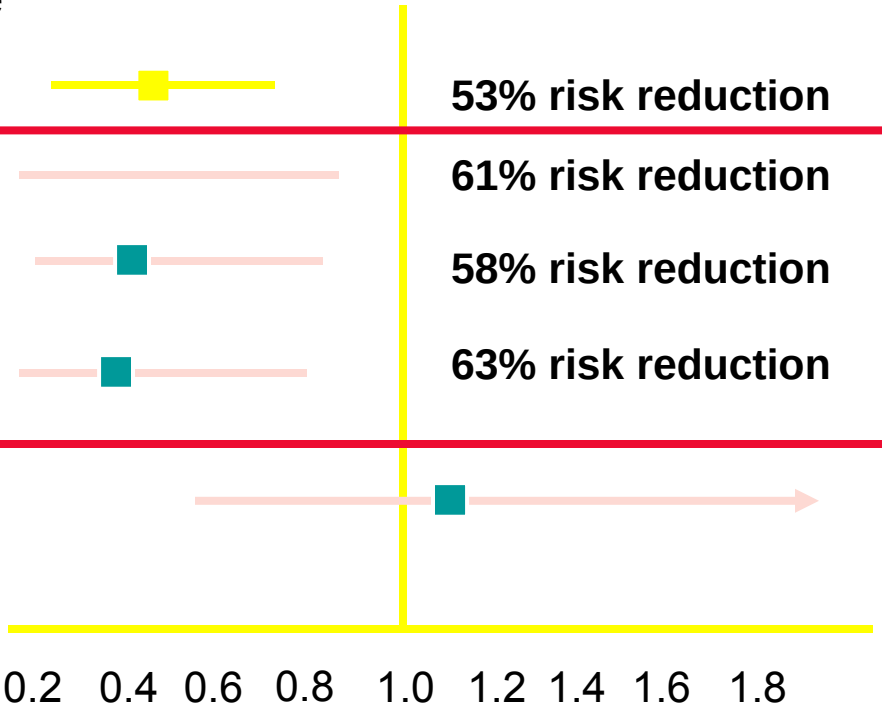
STENO: Changes in Risk Factors in Intensive vs. Conventional Therapy Groups



Gaede et al NJEM 2003;348:383-394

Intensive Multifactorial Intervention in Type 2 Diabetes

Complication	Risk ratio (95% CI)	p value	
1° Endpoint	0.47 (0.24 – 0.73)	0.008	**53% risk reduction**
Nephropathy	0.39 (0.17 – 0.87)	0.003	**61% risk reduction**
Retinopathy	0.42 (0.21 – 0.86)	0.02	**58% risk reduction**
Autonomic neuropathy	0.37 (0.18 – 0.79)	0.002	**63% risk reduction**
Peripheral neuropathy	1.09 (0.54 – 2.22	0.66	



INTENSIVE better CONVENTIONAL better

1° endpoint: CVD death, non-fatal MI, CABG, PTCA, non-fatal stroke, amputation, any bypass

Gaede P et al. *NEJM* 348:5, 2003. Leiter LA. Diabetes Res. Clin Practice. The role for lipid lowering for microvascular complications.

Summary and Conclusions: Disease Modifying Failure in Diabetic Neuropathies

- Diabetic Neuropathies are heterogeneous and may involve small and large fibers, with damage to each fiber producing its own constellation of features and requiring their own endpoints
- Hyperglycemia control is clearly effective in prevention and development of neuropathy in Type1 diabetes and the rate of deterioration is monotonic
- Multiple metabolic imbalances underlie the development of diabetic neuropathy particularly in type 2 diabetes
  - Hyperglycemia, dyslipidemia, and cardiovascular dysfunction are each independent risk factors for neuropathy
- If patients without DPN are to be recruited for study—scores of NC and heart rate with deep breathing

Optimizing Trials for DPN

- **Euglycemia improves responsiveness to ARIs prevents or ameliorates DSPN, do not select poorly controlled patients**
- **Patients with DPN use two attributes of NC and QSTs.**
- **Studies using large fiber measures need to be done for long times (4y) to show a treatment effect.**
- **Type 1 diabetic patients are preferable to type 2 diabetic patients because there is less variability of test results and polyneuropathy worsens to a greater degree and is monotonic**
- **The placebo effect of monotonic improvement of clinical signs and symptoms is of concern, ancillary adjunctive treatments patients in the placebo arm need to be controlled.**
- Choose a restricted number of centers
  - and expert examiners, trained, certified, using standard approaches,
  - and reference values and interactive surveillance of tests) are used.

Small fibers may be more plastic and non invasive endpoints may prove better than current large fiber measures.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Tumors: Patient-reported Outcomes and